REMARKS

Claims 8 and 9 have been cancelled and claims 1-7 amended. Claims 1-7 remain pending. Claims 1-7 have been generally amended to be drawn to method claims. Claim 4 has been additionally amended to delete "derivative" and more clearly define the subject matter of the claim. Support for the amendment to claim 4 may be found on page 18, lines 6-20 of the specification.

The specification has been amended to correct readily apparent typographical errors. For example, page 7, lines 5 and 6 and page 17, line 4 have been amended to correct citations to references. The correction of these typographical errors would be readily determined by one reading the specification based on the additional information given regarding the references.

Page 20, line 4 has been amended to correctly recite "autoimmume demyelinating disease" i.e. the subject matter of the invention.

Page 31, lines 8-9 has been amended to correctly recite "myelin basic protein." This correction is evident from the fact that (2) is the sequential step following (1) wherein preparation and administration of an emulsion of myelin basic protein is described.

As the identity and nature of correction of these typographical errors would be readily apparent to one skilled in the art reading the specification, correction of the errors does not add new matter to the specification. Entry of the amendments

is therefore respectfully requested.

Election of species

The Examiner makes the following election of species.

(a) a Fas derivative

(b) anti-Fas ligand antibody.

The Examiner asserts that the species (a) and (b) above lack unity of invention because they are not so linked to form a single inventive concept. Applicants traverse this election and examination of all of the claims is respectfully requested.

The claims have been amended to be drawn to methods of treating or preventing autoimmune demyelinating diseases by administering an apoptosis-suppressing substance. Claim 1 represents the common inventive concept of the invention. The nature of the invention is that administration of a substance which inhibits Fas-mediated apoptosis improves the pathology of demyelinating diseases. Both an anti-Fas ligand antibody and a Fas derivative, i.e. a polypeptide as defined in amended claim 4, function through the same mechanism in the method of the invention. As such, consideration of all of the claims is requested. However, for purposes of compliance with the response to the election of species, Applicants elect with traverse, the species (b) anti-Fas ligand antibody, i.e. amended claims 5, 6, and 7.

Should the Examiner have any questions regarding the present application, she is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069), in the Washington DC area, at (703) 205-8000.

A marked-up version of the amended paragraphs of the specification and claims showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Marked-up version

MARKED-UP VERSION

IN THE SPECIFICATION

The paragraph beginning on page 6, line 21 has been amended as follows:

Various studies have been recently conducted and reported for the relation between the multiple sclerosis and the apoptosis mediated by Fas/Fas ligand system. Sameer, D. et al. reported that they found the Fas ligand expressed in microglia cells and infiltrated T cells and the Fas expressed in oligodendrocytes, in the lesion of human multiple sclerosis (J. Exp. Med., vol. 184, pages 2361-2370, 1996). Kimberly A. et al. (J. Immunol., vol. [158] **159**, pages 3096-3099, 1997) and Hanspeter, W. et al. (J. Immunol., vol. [158] **159**, pages 3100-3103, 1997) suggested through animal experiment of multiple sclerosis using lpr and gld mouse, which are genetically deficient of the Fas and the Fas ligand, respectively, that the apoptosis mediated by the Fas/Fas ligand is involved in the multiple sclerosis. In the meanwhile, Eileen, A. et al. (J. Clin. Invest., vol. 98, pages 1602-1612, 1996) and Suzana, M. et al. (J. Exp. Med., vol. 186, pages 507-515, 1997) suggested through animal experiment of the multiple sclerosis using the same lpr and gld mouse that the apoptosis mediated by the Fas/Fas ligand is not involved in the multiple sclerosis. In other words, the relationship between the pathology of the multiple sclerosis and the apoptosis mediated by the Fas/Fas ligand system is still unknown and differently conceived depending on the investigator. In addition, efficiency

of the drug delivery to brain tissue is generally low, and it is utterly unknown whether the drug which suppresses the apoptosis by the Fas/Fas ligand administered to the body can suppress the Fas/Fas ligand-mediated apoptosis in the brain tissue, and it is also unknown whether the results will be the same as those obtained in the mouse genetically deficient of the Fas or the Fas ligand.

The paragraph beginning on page 16, line 23 has been amended as follows:

The anti-Fas ligand antibody and the anti-Fas antibody used in the present invention may be prepared by known process, for example, by the process described in International Patent Application Publication No. WO95/13293 and International Patent Application Publication No. WO[95/02290]**97/02290**. These publications are herein incorporated by reference.

The paragraph beginning on page 19, line 11 has been amended as follows:

Another preferable Fas derivative is the Fas having a deletion in its N terminal. Among these, Fas derivatives, the shFas(nd29)-Fc and the shFas(nd29)-hinge (International Patent Application Publication No. WO 97/42319) coded in plasmids (pM1304 and pM1317) included in the E. coli which were originally deposited in March 14, 1996 in National Institute of Bioscience

and Human Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) (Accession Nos. P-15514 and P-15515) and transferred from the original deposition to the international deposition on March 6, 1997 (Accession No. FERM BP-5854 and Accession No. FERM BP-5855) are derivatives including the extracellular domain of the known human Fas from which N terminal sequence of from 1st to 29th amino acid has been deleted, and these highly active derivatives are preferable examples of the effective component for the preventive and therapeutic agent of [cirrhosis] **autoimmune demyelinating diseases** of the present invention. This publication is herein incorporated by reference.

The paragraph beginning at page 31, line 6 has been amended as follows:

(2) Administration of anti-mouse Fas ligand antibody FLIM58

The rats were administered with 10 mg/kg of anti-mouse Fas ligand antibody FLIM58 7 days after [the splenocyte transplantation] **myelin basic protein** (day 7) i.v. via their tail vein. The control group was administered with equal dose of IgG purified from normal hamster γ-globulin. Each group consisted of 5 rats.

IN THE CLAIMS

Claims 8 and 9 have been cancelled.

Claims 1-7 have been amended as follows.

1. (Amended) [A preventative and therapeutic agent for] **A method for treating and preventing** autoimmune demyelinating diseases [containing] **which comprises administering to a patient in need thereof an effective amount of** an apoptosis-suppressing substance [as its effective component].

2. (Amended) [A preventative and therapeutic agent] **The method** according to claim 1 wherein said apoptosis-suppressing substance is a Fas antagonist.

3. (Amended) [A preventative and therapeutic agent] **The method** according to claim [1 or] 2 wherein said apoptosis-suppressing substance is a substance which suppresses Fas-Fas ligand binding.

4. (Amended) [A preventative and therapeutic agent] **The method** according to claim 1 wherein said apoptosis-suppressing substance is a **polypeptide of (a) or (b) as follows:**

(a) a polypeptide which comprises an amino acid sequence of a Fas protein that has been arbitrarily mutated at one or more amino acid residues by substitution, deletion and/or addition, and which has an activity of inhibiting Fas-mediated apoptosis; or

(b) a fusion polypeptide comprising (a) and another

polypeptide except (a) [Fas derivative].

5. (Amended) [A preventative and therapeutic agent] **The method** according to claim 1 wherein said apoptosis-suppressing substance is an anti-Fas ligand antibody.

6. (Amended) [A preventative and therapeutic agent] **The method** according to claim 1 wherein said autoimmune demyelinating disease is a disease associated with demyelination in central nervous system.

7. (Amended) [A preventative and therapeutic agent] **The method** according to claim 1 wherein said autoimmune demyelinating disease is at least one member selected from acute disseminated encephalomyelitis and multiple sclerosis.